Remarks

Claims 1-22 were previously canceled. Claims 23 and 24 were amended to specify that the formulation provides delayed and extended release and exhibits diminished incidence or reduced intensity relative to side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation. Support for the amendment is found at least page 9, lines 14-21.

Claim 27 was amended to specify that less than approximately 10% of the total milnacipran dose is released in one hour when the formulation is subjected to *in vitro* dissolution in 0.1 N HCl. New claim 42 was added specify that less than approximately 10% of the total milnacipran dose is released in two hours when the formulation is subjected to *in vitro* dissolution in 0.1 N HCl. Support for the amendment to claim 27 and new claim 28 is found at least in the Examples.

Claim 28 was amended to specify that the extended release of milnacipran is over a period of time that is between approximately four and approximately twenty-four hours. Support is found at least in the Examples and at page 28, lines 6 to 7.

Claim 36 was canceled.

Claim 37 was amended to specify that milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (F2782), individual enantiomers of para-hydroxy-milnacipran, mixtures of enantiomers of para-hydroxy-milnacipran, or pharmaceutically

acceptable salts thereof. Support for the amendment is found at least at page 13, line 29 to page 14, line 6.

Claim 38 was amended to specify that the delayed release is achieved by coating an extended release dosage form with at least one delayed release polymer which is insoluble in the acid environment of the stomach and is soluble in the neutral environment of the small intestine. Support for the amendment is found at least at page 24, line 16 to page 25, line 21 and the Examples.

New claim 43 was added. Support for new claim 43 is found at least at page 9, lines 6 to 7.

In the event that this amendment and response does not result in allowance of the claims, the undersigned respectfully requests a personal interview with the Examiner and her supervisor.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 23, 24, 27 and 28 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

Exxon Research and Engineering Company v. United States, 265 F.3d 1371 (Fed. Cir. 2001), stated the standard to be as follows: "If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2." *Id.* citing *Miles Labs, Inc., v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1994).

The court further stated that claims do not have to be plain on their face to be definite. Rather, "the claims need be amenable to construction, however difficult that task may be. If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.*

Analysis

The Examiner alleges that the phrase "diminished incidence or reduced intensity" in claims 23 and 24 is indefinite. Claim 23 defines a method of making a milnacipran formulation that provides delayed and extended release of milnacipran to produce a therapeutic effect over approximately 24 hours with diminished incidence or reduced intensity *relative to side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation.*

Claim 24 defines a method for delivering a therapeutic dose of milnacipran to a patient in need thereof, with diminished incidence or reduced intensity of common milnacipran side effects, comprising administering to the patient in need thereof a milnacipran formulation that provides delayed and extended release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation.

Common side effects associated with immediate release milnacipran formulations are listed in Table 1 on page 5 of the specification. The Examiner alleges that claims 23 and 24 do not provide any upper or lower limits. The claims specify that the formulation exhibits **reduced** incidence or intensity relative to one or more immediate release side effects. One of ordinary skill can evaluate whether a particular formulation meets this limitation by administering the formulation to one or more patients and evaluating the incidence and/or intensity of side effects relative to an immediate release formulation. One skilled in the art would understand the bounds of the claim when read in light of the specification. Accordingly, claims 23 and 24 are definite.

The Examiner alleges that the phrase "common milnacipran side effects" in claim 24 is indefinite. Common side effects associated with immediate release milnacipran formulations are listed in Table 1 on page 5 of the specification and on page 3, line 29 through page 4, line 16. The common side effects, including abdominal pain, nausea, headache and increased sweating, amongst other, are clearly defined in the specification. Further, the frequencies of these side effects following administration of an immediate release formulation are provided. One skilled in the art would understand the bounds of the claim, particularly when read in light of the specification. Accordingly, claim 24 is definite.

The Examiner alleges that the phrases "slow release" or "extended release" are indefinite. Without making any admissions and solely for the purpose of facilitating prosecution, claim 27 has been amended to specify that less than approximately 10% of the total *milnacipran* dose is

released in one hour when the formulation is subjected to *in vitro* dissolution in 0.1 N HCl. Claim 27, as amended, is definite.

The Examiner alleges that the phrase "wherein the defined period of time" in claim 28 is indefinite for lacking antecedent basis. Without making any admissions and solely for the purpose of facilitating prosecution, claim 28 has been amended to specify that the extended release of milnacipran is over a period of time that is between approximately four and approximately twenty-four hours. Claim 28, as amended, is definite.

Rejection Under 35 U.S.C. § 103

Claims 23-41 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,699,506 to Paillard *et al.* ("Paillard"), in view of U.S. Patent No. 6,066,643 to Perry ("Perry") further in view of U.S. Patent No. 6,380,200 to Mylari ("Mylari"). Claims 23-41 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,699,506 to Paillard *et al.* ("Paillard"), in view of WO 99/59593 to Michelson *et al.* ("Michelson") further in view of U.S. Patent No. 6,380,200 to Mylari ("Mylari") Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1,

17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Supreme Court did not obviate the requirement for the references to provide some motivation to combine as applicants have done, with a reasonable expectation of success. Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> "The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of

obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Analysis

Independent claims 23 and 24 have been amended to define a milnacipran formulation that provides delayed and extended release and to specify that the formulation exhibits diminished incidence or reduced intensity relative to one or more side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation. Support for the amendment is found at least at page 9, lines 14-21 and page 10, lines 3-4.

1. Paillard in view of Perry and Mylari

As discussed above, the Court recently reaffirmed the *Graham* factors, which are analyzed below:

(a) Determining the scope and contents of the prior art

Paillard

Paillard describes a pharmaceutical composition with *prolonged release* for oral administration of a single daily dose of milnacipran of 60 to 140 mg (abstract). The composition

contains a plurality of microgranules each containing an active microsphere containing a saccharose and/or starch nucleus of a size between 200 and 2000 μm and containing 150 to 1000 μg of milnacipran and a binding agent (abstract). Each microgranule is coated with a film having a base of at least one polymer insoluble in water but permeable to physiological fluids of a thickness between 20 and 100 μm (abstract). The composition has the following *in vitro* release profile: between 10 and 55% of the dose released in 2 hours; between 40 and 75% of the dose released in 4 hours; between 70 and 90% of the dose released in 8 hours; and between 80 and 100% of the dose released in 12 hours (abstract). This release profile is achieved using only one type of microgranule per formulation (col. 3, lines 20-25).

Paillard does not disclose or suggest a milnacipran formulation that provides delayed **and** extended release of milnacipran with diminished incidence or reduced the intensity of one or more immediate release milnacipran side effects. The coating agents used in Paillard are methacrylic acid copolymers of the poly(ethyl acrylate, methyl methacrylate) type in aqueous dispersion marketed under the name Eudragit NE30D, or of the poly(ethyl acrylate, methyl methacrylate, trimethylammoniumethyl methacrylate chloride) type in organic solvents (RS 100 or RL100) or in aqueous dispersion (RS30D/RL30D), whose permeability depends on the amount of ammonium groups (RL>RS) (col. 6, lines 52-58). Ethyl cellulose can also be used (col. 7, lines 1 to 2 and 10-13). As shown in the attached product descriptions and the article entitled "Guidelines for Formulation Development and Process Technology for Sustained Release Coatings" from the Degussa website, these polymers are extended or sustained release

polymers, not delayed release polymers. For example, Eudragit RL, RS, and NE polymers are described as sustained release polymers in the document entitled "Acrylic Polymers for Controlled Release", a copy of which is enclosed. Accordingly, Paillard discloses compositions which provide extended release, not a mixture of delayed and extended release of milnacipran as required by the claims, as amended.

Perry

Perry describes a method for producing a potentiating effect on a therapeutic action of an agent which is selected from a serotonin re-uptake inhibitor, a nor-epinephrine re-uptake inhibitor, both a serotonin and a norepinephrine re-uptake inhibitor, and an atypical antidepressant (abstract). The method involves co-administering an effect amount of moxonidine, or a pharmaceutically acceptable salt thereof, which itself can cause side effects, to potentiate the effects of an active agent (abstract). Compositions may be formulated so as to provide quick, sustained, *or* delayed release of the active ingredient after administration to the patient (col. 6, lines 46-49). Perry does not disclose or suggest a milnacipran formulation that provides delayed and extended release of milnacipran with diminished incidence or reduced the intensity of one or more immediate release milnacipran side effects, as required by the claims.

Mylari

Mylari describes methods, pharmaceutical compositions, and kits containing an aldose reductase inhibitor (ARI), a prodrug thereof or a pharmaceutically acceptable salt of an ARI or

prodrug thereof and a selective serotonin reuptake inhibitor (SSRI), a prodrug thereof or a pharmaceutically acceptable salt of an SSRI or prodrug thereof (abstract). Mylari is silent regarding modified release formulations. Mylari does not disclose or suggest a milnacipran formulation that provides delayed and extended release of milnacipran with diminished incidence or reduced the intensity of one or more immediate release milnacipran side effects, as required by the claims as amended.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The Claimed Methods

The claimed methods involve administering a milnacipran formulation that provides delayed **and** extended release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation. Release of milnacipran is delayed until the formulation passes through the stomach thus minimizing locally mediated side effects. Extended

release of milnacipran lowers the slope of the plasma curve and increases the T_{max} to effectively decrease centrally mediated side effects and provided for once-a-day administration of the drug.

The release profile is characterized in that less than 10% of the total of milnacipran is released over a period of one hour *in vitro* (claim 27) or two hours *in vitro* (claim 42). The method involves administering a formulation that provides milnacipran blood plasma levels that are characterized by a T_{max} at 4-10 hours, and C_{max} below approximately 3000 ng/ml (claim 29), preferably below 2000 ng/ml (claim 30), and more preferably below 1000 ng/ml (claim 31). The formulation can further comprise at least one other active agent (claims 32 and 33).

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, none of the references alone or in combination discloses a milnacipran formulation that provides delayed and extended release of milnacipran, nor kits containing the same, nor is there any teaching leading one of skill in the art to modify to what applicants' claim.

The formulations described in Paillard are extended release formulations as shown by the enclosed documents describing extended release polymers. In contrast, the claims require a milnacipran formulation that provides extended **and** delayed release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more side effects resulting from

administration of the same dose of milnacipran administered in an immediate release formulation.

The prolonged release characteristics of the formulations of Paillard are imparted by coating minispheres of milnacipran with film-forming extended release polymers insoluble in water but permeable to physiologic fluids and which allows milnacipran in solution to pass through by diffusion phenomena (col. 6, lines 45-48). Many different types of coating polymers that provided extended release are disclosed (col. 6, line 49 – col. 7, line 6); however, Paillard does not disclose or suggest using any specific combinations of coatings, let alone a combination of extended release and delayed release as required by the claims.

Further, Paillard fails to disclose diminishing locally and/or centrally mediated side effects. Merely stating that a drug can be administered using a sustained release formulation is not sufficient to establish that the formulation is effective to reduce side effects while still maintaining efficacy.

Table 1 in the present application shows that the incidence of certain adverse events associated with immediate release milnacipran formulations increases with dosage. As further shown in Table 1, a linear relationship does not exist between dosage and the incidence of the side effect. For example, the frequency of nausea decreased when increasing dosage from 50 mg/day twice daily to 100 mg/day twice daily, and then increased when increasing the dosage from 100 mg/day twice daily to 200 mg/day twice daily. The effect of the dose of milnacipran on the incidence and severity of side effects was not predictable at the time the present

application was filed in view of this data. Only through a thorough understanding of the relationship between therapeutic dose and blood plasma levels can a modified dosage form be designed to reduce or diminish locally and centrally mediated side effects (page 7, lines 10-13). Specific pharmacokinetic parameters reflecting this understanding are defined in claims 29-31. Paillard does not disclose or suggest formulations a formulation exhibiting the parameters defined in claims 29-31.

The Examiner concedes that Paillard does not disclose or suggest the reduction of side effects. However, the Examiner alleges that the formulation of Paillard would provide beneficial therapeutic effects as desired by the Applicant. A beneficial therapeutic effect is not the same as reducing the incidence or intensity of side effects. As discussed above, milnacipran causes both locally mediated and centrally mediated side effects. The combination of delayed release and extended release minimizes both of these types of side effects as shown in the bioavailability study described in the attached declaration. Accordingly, it is unlikely that the extended release formulations of Paillard would minimize or prevent locally mediated side effects of milnacipran.

Therefore, one of ordinary skill in the art, at the time the present application was filed, would not have an expectation of success that an extended release formulation of milnacipran could be developed that would deliver an efficacious dose while also reducing the incidence and/or severity of untoward side effects relative to immediate release milnacipran formulations.

Perry discloses methods for potentiating the therapeutic action of agents by co-administration of moxonidine (abstract). Perry does not disclose a formulation that provides

delayed and extended release of milnacipran. Further, Perry does not disclose milnacipran formulations that with diminished incidence or reduced intensity relative to one or more side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation. Perry is only concerned with formulations that potentiate efficacy of active agents and is silent with respect to effects on reducing the incidence or diminishing the intensity of any side effects. Perry does not cure the deficiencies of Paillard.

Mylari is also silent regarding modified release formulations. Mylari does not cure the deficiencies of Paillard and Perry.

The references cited by the Examiner do not contain all the elements of the claims. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 23-41. Accordingly, claims 23-41 are not obvious over Paillard in view of Perry and further in view of Mylari.

Declaration showing unexpected results

A Declaration under 37 C.F.R. § 1.132 by Dr. Martin Keller demonstrating unexpected results is attached to this amendment and response. This declaration establishes that it was not obvious to develop a once-a-day formulation that would deliver a therapeutic dose of milnacipran while reducing the incidence and severity of side effects relative to immediate release milnacipran.

In the declaration, Dr. Keller describes the unique tolerability challenges that milnacipran presents relative to SSRIs. Dr. Keller further establishes that the design of the claimed

milnacipran formulations only arose through the inventors' extraordinary understanding of the pharmacology and pharmacokinetics of NSRIs and intuition that led to their hypothesis that milnacipran's side effects may be both locally *and* centrally mediated. The data presented in the declaration demonstrate the unexpected result that formulations of milnacipran that combine a delayed release component to alleviate locally mediated side effects with an extended release formulation that lowers the slope of the plasma curve and increases T_{max} to effectively decrease centrally mediated side effects result in a favorable tolerability profile. In fact, in a bioavailability trial, none of the subjects at any given time experienced any of the common milnacipran side effects such as nausea, vomiting, sweating and tremors. Importantly, this study was conducted under fasting conditions, when milnacipran side effects are normally more pronounced.

These unexpected results are strong indicia of non-obviousness.

2. Paillard in view of Michelson and Mylari

(a) Determining the scope and contents of the prior art

Paillard and Mylari are discussed above. Michelson describes a method for treating depression including administering to a patient an effective amount of a first component which is a 5-HT_3 receptor antagonist, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor, wherein improvement in sexual dysfunction and/or reduction is gastrointestinal side effects is alleged (abstract). Michelson is attempting to reduce side effects by potentiating the effect of one active agent with a second active agent. Michelson

does not disclose or suggest a milnacipran formulation providing delayed and extended release of milnacipran.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The claimed methods are discussed above.

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, Paillard and Mylari, alone or in combination, do not disclose or suggest a milnacipran formulation that provides delayed and extended release of milnacipran. Paillard and Mylari do not disclose or suggest a milnacipran formulation that provides delayed and extended release of milnacipran with diminished incidence or reduced intensity of side effects. Michelson discloses reducing side effects by potentiating the effects of a first active agent with a second active agent. Michelson does not disclose a formulation that provides delayed and extended release of milnacipran. Therefore, Michelson does not cure the deficiencies of Paillard and Mylari.

As stated above with respect to Perry, the claims of the present application require a milnacipran formulation *per se* that provides delayed and extended release of milnacipran to produce a therapeutic effect over approximately 24 hours, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In contrast, the formulations described by Michelson *require* an additional active agent to reduce gastrointestinal side affects. Dependent claims of the present application specify additional active agents that may be administered with milnacipran, but these additional agents are not required to produce the characteristics of the claimed milnacipran formulations. Therefore, in addition to failing to provide the elements missing from Paillard, Michelson does not provide one of ordinary skill in the art with a reasonable expectation of success for producing a milnacipran formulation with the claimed properties.

Michelson does not cure the deficiencies of Paillard and Mylari. Further, the references, alone or in combination, do not disclose or suggest the release profile defined in claim 27 or the pharmacokinetic parameters in claims 29-31. The Examiner has failed to establish a *prima facie* case of obviousness. Therefore, claims 23-41 are not obvious over Paillard in view of Michelson and Mylari.

Declaration showing unexpected results

As discussed above, a Declaration under 37 C.F.R. § 1.132 by Dr. Martin Keller demonstrating unexpected results is attached to this amendment and response. The unexpected results presented therein, and discussed above, are strong indicia of non-obviousness.

Double Patenting Rejection

Claims 23-41 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of Application Serial No. U.S.S.N. 10/691,936.

Without making any admissions and solely for the purpose of facilitating prosecution, Applicants will file a terminal disclaimer once the claims of the present application are in condition for allowance.

Allowance of claims 23-43, as amended, is respectfully solicited.

Respectfully submitted,

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